AMNIOCENTESIS AS A TOOL IN MANAGEMENT OF PRETERM PREMATURE RUPTURE OF THE FETAL MEMBRANES

EMILIO J. JUNCOSA

1984

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Amniocentesis as a Tool in Management of Preterm Premature Rupture of the Fetal Membranes

by

Emilio J. Juncosa

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1984

Una tarde partí

Hacia extraña nación

Pues lo quiso el destino,

Pero mi corazón

Se quedó frente al mar

En mi Viejo San Juan.

Noel Estrada

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ABSTRACT

147 patients with preterm premature rupture of membranes were retrospectively studied to determine what clinical parameters would predict a positive amniotic fluid culture and to assess the usefulness of amniocentesis in managing patients with preterm PROM.

77 patients with successful amniocentesis were divided into two groups: those with negative amniotic fluid cultures and those with positive cultures. Maternal temperature, WBC count, neutrophil cound, band count, absolute neutrophil count and uterine irritability on admission were not predictive of a positive amniotic fluid culture. Similarly, at the time of amniocentesis, the following parameters were not predictive of a positive amniotic fluid culture: maternal age, gestational age, temperature, WBC count, neutrophil and band counts, absolute neutrophil count and presence of contractions. Gram stain of the amniotic fluid was 61.9% sensitive and 91.8% specific in predicting a positive culture. A positive culture did not correlate with increased maternal morbidity but correlated with considerably higher rates of RDS and low Apgar scores in newborns. This study under-

scores the importance of amniocentesis as an aid in managing the patient with preterm PROM.

Premature rupture of the fetal membranes (PROM) occurs in 2.1-12.5% of all pregnancies according to several large reported studies (1-8). (See Table 1). It is an event that can result in serious maternal and fetal complications. Difficulty in management is greatest in the preterm gestation, where the risk of infection of the amniotic cavity, a common complication of expectant management, must be weighed against the risk of prematurity, resulting from early delivery. Prematurity is still responsible for about half of all infant deaths, and 40% of these are brought about following labor after PROM (9). The rationale for prompt delivery of the fetus is prevention of infection, whereas expectant management attempts to enhance neonatal outcome by increasing fetal viability.

A study of the problem of PROM should include a discussion of the anatomy and physical properties of the membranes in addition to discussing the causes and effects of PROM. Is infection a cause or a consequence of PROM? What management strategy best maximizes maturity without increasing the incidence of infection? Does PROM per se enhance pulmonary maturation and thus decrease the risk of neonatal Respiratory Distress Syndrome (RDS)? How can amniocentesis aid in the management

of PROM?

Anatomy of the Fetal Membranes

The fetal membranes, the amnion and the chorion, extend beyond the lateral margin of the placenta, and with the placenta, form the closed cavity containing the fetus. At term the amniotic cavity contains approximately one liter of amniotic fluid.

Microscopically, from inside out, the membranes consist of the amnion, the chorion, and the decidua. The amnion, a single layer of cuboidal or cylindrical cells on a basement membrane over a thin collagenous layer, contains occasional mesenchymal cells. The attachment to the next layer is very loose, and the amnion is readily peeled off. The zone of contact is actually a virtual cavity representing a remnant of the extraembryonic coelom. The chorion (chorion laeve - smooth chorion), a thicker, fibrous avascular layer, contains, like the amnion, multipotential mesenchymal cells with both fibroblastic and phagocytic properties. The decidua, a well-vascularized maternal tissue, contains occasional lymphocytes.

The fetal surface of the placenta is normally shiny with a bluish color. From the fetal surface out towards

the maternal surface, the following layers are encountered: the amnion, the placental chorion, the villi and intervillous space, and the basal decidua. There are no polymorphonuclear cells in the normal amnion, chorion, or placenta (10).

When the amnion at term is examined by transmission electron microscopy, pedicles can be seen extending into the basement membrane. The intercellular junctions are formed by desmosomes and a labyrinthine channel system.

The basement membrane seems to play a primordial role in preserving the intact amniotic cavity, and the presence of pedicles is suggestive of active transport (11).

Physical Properties of the Membranes and Premature Rupture

There has been considerable interest in the physical properties of membranes which rupture prematurely. The amnion, which is rich in collagen, is the main load-bearing component of the membranes (12). MacLahan (13) determined that the mean bursting pressure of the membranes was 393 mm Hg. Several studies (14) have failed to show differences in the physical properties of prematurely- versus appropriately-ruptured membranes. Skinner et al (12), however, found that the collagen content of the human amnion decreases significantly during the

last eight weeks of pregnancy and found that this decrease was also observed, at an earlier gestational age, in pregnancies with PROM. To determine whether the relative decrease in the collagen content of prematurely ruptured membranes was a cause rather than an effect of PROM, the authors investigated the effect of the duration of ruptured membranes on their collagen content. They found a slight but significant increase in the collagen content of the amnion as the latent period between rupture and onset of labor increased. The collagen values were normalized to a single gestational age to eliminate bias due to a possible association between long latent period and early PROM. Their results suggest that rupture of the membranes does not in itself enhance collagen degradation, but that weakening of the amnion in preparation for rupture may be determined partly by factors controlling the synthesis and degradation of collagen. Wideman et al (15) suggest that PROM may be associated with ascorbic acid deficiency. In their series of 288 pregnancies, 14.6% of patients with ascorbic acid levels of less than 0.20 mg% had PROM as compared to 1.5% of patients whose plasma ascorbic acid levels were greater than 0.60 mg%. Skinner and Liggins (16) found that the concentration of sulphated glycosaminoglycans decreased significantly near term, and again found a statistically significant

earlier decrease in pregnancies with PROM. Unfortunately, the relative contribution of these factors in individual cases of PROM has not been determined. Studies of the physical properties of the membranes have been criticized (17) because of differences in measuring techniques, possible deterioration of membrane preparations, and inherent difficulties with establishing adequate controls.

Etiology of PROM

The etiology of PROM has not been yet determined. Some ruptures have a clear-cut cause, such as an incompetent cervix, polyhydramnios or trauma (18), but in some cases there is no explanation. Other predisposing factors which have been proposed include cervicitis, amnionitis, placenta previa, genetic abnormalities of the fetus, fetal malpresentations, increased intrauterine pressure due to multiple gestation, previously induced abortion, abruption, coitus, and vaginal infections (14), as well as the intrinsic abnormalities of the membranes discussed in the previous section. Naeye and Peters (18) studied 6613 pregnancies that ended before term to determine whether amniotic fluid infections could be a cause as well as a complication of PROM. They found that on pathological examination, amniotic fluid infections

were two to three times more common when the fetal membranes ruptured just before labor started than when they ruptured just after the onset of labor. They also found that although coitus in the preceeding month did not increase the chance of PROM it increased the histological severity of the infections associated with PROM. Parity did not increase the chance of PROM but again the infections in multiparas were pathologically more severe than in primiparas. The possibility that amniotic fluid infection may be a cause of PROM had been suggested in 1972 by Cederqvist (19) who found that 63% of cord bloods in infants born after PROM had increased levels of IgM or IgA, suggesting that these fetuses had experienced infections of some duration.

There thus seem to be two distinct sets of patients who rupture their membranes prematurely: those who are not infected at the time of PROM and who may remain uninfected for several weeks, and those whose premature rupture seems to have been caused by a preexisting amniotic fluid infection.

In a study of 10,640 pregnancies, Naeye (20) found that the recurrence risk of PROM in the next pregnancy was 21%. He found an incidence of only 4% in pregnancies which followed a normal pregnancy. Preterm PROM increased

significantly with parity, but only after the third pregnancy.

Latent Period Between PROM and Delivery

With increasing time interval between PROM and delivery, the risk of developing intrauterine infection becomes greater (9). The term fetus does not suffer significantly in most cases, since over 80% of patients with PROM at term will go into spontaneous labor before 24 hours. Presently, induction with oxytocin is almost standard procedure for term patients with PROM who are not in labor after 12 to 24 hours after rupturing membranes.

About 35-50% of patients with PROM before 36 weeks gestational age will go into spontaneous labor within 24 hours (9). All authors agree that there is an inverse relationship between length of gestation and latent period between rupture of membranes and delivery. After 24 hours of PROM, the incidence of amnionitis rises to 10-30% (9). Breese (21) showed that diminishing fetal size and increasing latent period are proportional to each other and showed that mortality also correlates with both diminishing fetal size and increased duration of the latent period. Hence, the premature fetus, who needs the extra time *in utero* to achieve

maturation, is the one most at risk for developing infection due to a longer latent period.

In 1982 Mueller-Heubach et al (22) showed that there was only a slightly higher risk of infection when the time elapsed between rupture and delivery exceeded 24 hours, and marked decrease in the incidence of infection was seen with advancing gestational age. The highest rate of infection in their series was less than 15% and occured in pregnancies between 27 and 30 weeks. The authors showed that the length of the latent period was a far less important factor than gestational age for the risk of neonatal infection, which they defined as culture-proven septicemia or meningitis, or autopsy-proven pneumonia.

PROM Before and After 35 Weeks Gestational Age

The decision between expeditious delivery and expectant management of a patient with PROM involves evaluating the risk of infection versus potential improvement in neonatal outcome from extended *in utero* time. The more advanced the gestation, the more mature the fetus will be and the less the risk of infection.

Thus, in order to determine which fetuses to deliver without waiting, it is necessary to compare the risk of death in the neonatal period of uninfected

neonates at various gestational ages with the risk of neonatal death resulting from infection at those same gestational ages. In their study, Mueller-Heubach et al (22) found that until 35 weeks gestation, the risk of a non-infected infant dying from prematurity or other causes is greater than the risk of that infant dying from infection. At 35 weeks gestation and more, the risk of neonatal death caused by infection is slightly higher than the risk of death from other causes.

Therefore, the authors suggest than in patients over 35 weeks gestation with PROM, delivery should be accomplished without delay. In addition, it has been shown that prolongation of the latent period over 24 hours in the term gestation is associated with an increase not only of perinatal deaths but also of intrapartum fever and maternal endometritis (23).

PROM and the Neonatal Respiratory Distress Syndrome

There is no general agreement concerning the relationship between PROM and the neonatal respiratory distress syndrome (RDS). There is a large volume of literature supporting and disclaiming the hypothesis that rupture of the membranes of more than 12 to 16 hours *per se* accelerates fetal lung maturation in the preterm pregnancy (24). (See Table 2). In a major

study, Jones et al (25) found no relationship between PROM and decreased RDS. The authors studied 16,458 consecutive births in which there were 205 cases of PROM. PROM was defined as rupture of membranes occuring more than 24 hours before delivery, and RDS was defined as respiratory distress in the neonate with tachypnea, intercostal retractions and grunting beginning within the first three hours of life and lasting for at least 24 hours or until death. A control group of infants of similar gestational age without PROM was established. The study has been criticized (9) on the grounds that gestational age was established only by menstrual history and by the failure to further evaluate the effect of respiratory failure in the infants involved.

In 1978 Berkowitz et al (26) reviewed the records of 340 infants of 36 weeks gestational age or less admitted to Yale's Newborn Special Care Unit born after PROM. Twins and infants of diabetic mothers were excluded from the data analysis. The authors found that rupture of membranes over 16 hours duration was associated with a statistically significant reduction in the incidence of RDS in infants of 31 weeks gestational age or more. The association between PROM in excess of 16 hours and survival, however, was only statistically significant for infants of 33 weeks gestational age or more.

In this study PROM was defined as rupture of membranes prior to the onset of labor. The diagnosis of RDS was made on radiologic, laboratory, and clinical manifestations of the disease. Wender et al (27) reported a case of a twin born at 34 weeks with intact membranes who developed RDS at birth while the other twin, who had had prolonged rupture of membranes, did not develop RDS.

Mead (24) has noted several inconsistencies in the reports supporting the association between PROM and decreased RDS. He points to the fact that in 1972, Alden et al (28) showed an association between increased survival of infants weighing less than 1000 gm and PROM. Nevertheless, there was no decrease in the incidence of RDS in these infants when compared to a weight-matched control group without PROM. Miller et al (29) showed a decrease in RDS in infants weighing between 1000 and 1500 gm with an increase in the duration of ruptured membranes. He found that the incidence of RDS was not altered by PROM when the birth weight was more than 1500 gm. Moreover, as with Berkowitz's series, perinatal mortality remained unaltered with an increase in the duration of PROM. Seidl (30) showed a significanly lower incidence of RDS in newborns of 33 to 36 weeks gestational age with PROM of only one hour duration or more

when compared to infants of similar gestational ages with PROM of less than one hour duration. Worthington (31) suggested that fetal lung maturation occurred before membranes ruptured since he found that PROM was associated with a lower incidence of RDS regardless of the length of the latent period.

Presently, the protective effect of PROM against RDS is not universally accepted, but the validity of this association must be considered as a potential significant variable in studies attempting to induce pulmonary maturation in cases of PROM.

Management of PROM

The management of PROM in preterm pregnancies is a major controversy in modern perinatology. There is little controversy when PROM occurs after 35 weeks gestation, when most fetuses can be safely presumed to be mature, and delivery is indicated (23).

In the preterm pregnancy complicated by PROM, the leading cause of neonatal morbidity and mortality is RDS. A large body of data from recent studies (32) focusing on infection-related ouctomes strongly suggests that although the incidences of perinatal death overall and perinatal death due to infection, neonatal sepsis, intrapartum fever and maternal endometritis are increased in patients

delivering before term compared to those delivering at term, the risks due solely to PROM are insignificant compared with the risk associated with preterm delivery per se (RDS, intraventricular hemorrhage, apnea and bradycardia, hyperbilirubinemia, etc.). Thus prematurity, not infection, poses the greatest risk to the neonate in cases of PROM before term, and recent efforts have focused on prolonging pregnancy or preventing or ameliorating RDS with the use of corticosteroids.

When PROM occurs before 35 weeks gestation, a management strategy must be selected. Advocates of conservative management argue that delaying delivery in patients with PROM, no signs of infection, and no documented fetal pulmonary maturity will result in significant pulmonary as well as general fetal maturation. As discussed above, several studies (9,22,23) of conservative management of PROM have shown that the risk of prematurity is greater than the risk of infection, and prematurity causes a far greater number of neonatal deaths than infection in neonates delivered after PROM. Unfortunately, in series reported to date, less than 10% of patients with PROM in a preterm pregnancy will have a latent period of one week or more (34). Even with the use of tocolytics, delay in delivery for six days or more is achieved in only 10.5-38.5% of patients(17). Thus,

expectant management of preterm PROM does not appear to have adverse effects on the incidence of maternal or neonatal infection but is not very effective in achieving significant extensions of intrauterine life.

Aggressive management of preterm PROM generally implies the use of corticosteroids followed by delivery within 24 to 48 hours. In a landmark paper in 1972, Liggins and Howie (35) showed that a significant reduction in RDS was achieved in newborns of women treated with betamethasone and in whom delivery is between 28 and 32 weeks provided that the interval between treatment and delivery is more than one day but less than one week. No adverse effects on neonates or mothers were noted. Several series have since appeared and widely varying incidences of RDS after steroid therapy have been reported (17). In addition, a major concern with steroid therapy in pregnancies with PROM is the masking of maternal and fetal infection. Glucocorticoid therapy will produce leukocytosis for up to 48 hours after the last dose, thus eliminating this indicator of infection. However, Kuhn et al (36) found no significant differences in rates of infectious morbidity for mothers and infants in steroid-treated and control groups. Mead (37) also found no differences in morbidity in newborns born to steroid-treated and control groups.

Usefulness of Amniocentesis in Patients with PROM

It is obviously desirable to be able to predict which patients with PROM are destined to develop clinical chorioamnionitis so that appropriate steps can be taken to ensure early diagnosis and minimize morbidity. The classical clinical findings of chorioamnionitis may not be present in all cases. Fetal tachycardia, leukocytosis and tachycardia in the mother, fever, uterine tenderness and purulent, foul-smelling discharge are late-appearing signs indicating a well-established infection (32). Before attempting to prolong pregnancy in the preterm patient with PROM, an effort should be made to rule out occult intrauterine infection. In the absence of clinical signs of infection, Gram stain and culture of the amniotic fluid obtained transabdominally are the only reliable methods for diagnosing incipient chorioamnionitis (38,39). Garite and Freeman (38) found that a positive Gram stain for bacteria on a smear of amniotic fluid obtained by amniocentesis was 81% sensitive and 78% specific in predicting clinical infection. Unfortunately, the study group was composed of only 91 pregnancies and fluid was obtained in only 51% of these. The authors updated their results in 1982 (39) and found

that in afebrile patients, amniocenteses positive for bacteria on Gram stain and/or with subsequent positive culture correlated with subsequent development of antenatal maternal fever. Fetal tachycardia, maternal leukocytosis, and uterine contractions were not predictive of intrauterine infection in afebrile patients. Hill (40) found good correlation between a positive culture and subsequent chorioamnionitis, but bacteria on the smear did not correlate well with the development of neonatal infection. Leukocytes on the amniotic fluid smear is generally thought not to be a significant clinical finding (39,40).

In addition to bacterial studies, fluid obtained at amniocentesis can be used to test for fetal pulmonary maturity (41). The ratio of lecithin to sphingomyelin (L/S ratio) and the presence of phosphatidyl glycerol (PG) in the amniotic fluid are the most commonly used measures of fetal pulmonary maturation.

Amniocentesis is not an entirely harmless procedure. Potential complications include fetal trauma, bleeding from injured cord or placental vessels, initiation of labor or introduction of infection. These complications are unusual, however, and the finding of bacteria on Gram stain of amniotic fluid appears to be a rapid, practical and precise technique for iden-

tifying patients with early chorioamnionitis.

Chorioamnionitis

Infection of the amniotic sac, also referred to as amnionitis, chorioamnionitis, intraamniotic infection, amniotic infection or intrauterine infection is diagnosed clinical in 0.5-1% of all pregnancies but in 3-35% of those with rupture of membranes of more than 24 hours duration (42). In addition, over 50% of placentas of stillbirths show histological evidence of chorioamnionitis at autopsy (43).

Infection of the fetal membranes most commonly results from ascentind infection from the cervicovaginal system (44). The histogenesis of chorioamnionitis always shows the same pattern (10): The exudative reaction begins in the large chorionic vessels of the chorionic plate or within the umbilical cord vessels themselves. Initially there is margination of leukocytes within the vessels, followed by transmural migration of the cells. The leukophilic reaction occurs beneath the amniotic epithelium and the integrity of the amnion is generally preserved, except for focal areas where necrosis of the cells and spread of infected material into the amniotic cavity may occur. As a consequence of the pathological events, infection of the fetus may ensue. Most commonly, fetal

infections results from ingestion or aspiration of infected amniotic fluid, but it can arise through hematogenous spread via the infected fetal vessels of the chorionic plate or cord, resulting in primary fetal septicemia.

Once chorioamnionitis is diagnosed, most authors support the need for prompt delivery and initiation of antibiotic therapy. Gibbs et al (45) found no correlation between fetomaternal outcome and interval between diagnosis of chorioamnionitis and delivery, provided that delivery was accomplished within 24 hours of diagnosis.

Several recent studies have employed prophylactic antibiotics in patients with PROM, but few did so in standardized fashion (17). Habel et al (46) studied 100 infants born after 24 or more hours of PROM where antiobiotics had been used prophylactically. They found that infections were few but fungal infections were increased compared to a control group with PROM but no antibiotics. The authors concluded that prophylactic antibiotics were not useful in PROM. In addition, use of antibiotics before delivery complicates management of the newborn, since neonatal blood cultures may be negative despite neonatal infection (9). Recent interest in the use of prophylactic antibiotics in PROM has been less than in the past.

Neonatal Infection After PROM

Chorioamnionitis is a significant predisposing factor of early onset septic complications in the neonate such as pneumonia and meningitis.

Septicemia develops quite readily in newborns either as a primary entity or as a sequela of infection during intrauterine life. Commonly, it is produced by enteric organisms characterized by their minimal virulence in the adult (44). Infection with organisms of higher virulence, such as the streptococcus, is becoming less common, and presently Group B streptococcus is the only streptococcus still important in the neonatal period. Staphylococcus is still important and can cause fulminant neonatal sepsis (47).

Neonatal septicemia usually does not present clinically with the high fever, leukocytosis and prostration characteristic of infections in later life. There may be leukopenia, thrombocytopenia, or hypothermia (47). Many infants give a clinical impression of sepsis but only in a minority of these can the diagnosis be confirmed by blood culture (48).

Garite and Freeman (38) found that duration of maternal fever and chorioamnionitis are not statistically related to perinatal mortality. Siegel and MacCracken

found an incidence of culture-proven septicemia in only 5% of neonates born after chorioamnionitis had been diagnosed in the mother.

After the 36th week of pregnancy, healthy infants of healthy mothers born after PROM may be treated as uninfected neonates as their infection risk is minimal, according to Eisenberg and Krauss of Cornell (49). Before this gestational age, the authors suggest that infants should receive a full septic workup, and antibiotic therapy should be instituted until culture results are reported as negative.

Management of PROM at Yale-New Haven Hospital

At Yale-New Haven Hospital, patients who rupture their membranes prematurely are managed as follows: A sterile speculum examination of the cervix is performed on admission and the presence of ruptured membranes is confirmed by fluid crystallization (fern test), nitrazine, and the presence of amniotic fluid pool in the vagina. If the patient is without clinical signs of infection and is over 36 weeks gestation with a negative glucose tolerance test, then she is induced is no spontaneous labor ensues after 6 to 12 hours.

In the clinically uninfected patient with PROM before 36 weeks gestation, every effort is made to ob-

tain amniotic fluid by amniocentesis after gestational age and fetal weight are estimated by ultrasound examination. If amniocentesis is successful, fluid is sent for L/S ratio, PG, Gram stain and bacterial cultures. If the Gram stain is negative for bacteria, the patient is placed on bedrest and is followed closely with frequent determinations of vital signs, daily leukocyte and differential blood counts, and observation for any signs of labor. If the L/S or PG studies determine that there is fetal pulmonary immaturity, an expectant management plan is instituted with an attempt to prolong the pregnancy sufficiently for fetal maturity to ensue. Beta-mimetic agents and magnesium sulfate are used as tocolytics if the patient shows signs of labor but no clinical signs of infection. Repeat amniocenteses are performed at weekly intervals in the absence of labor to ensure that the amniotic fluid is not colonized and to follow fetal pulmonary maturity parameters. Amniocentesis is also repeated if the patient shows signs of labor or possible infection. Once fetal pulmonary maturity is documented, tocolytics are discontinued if they were being used and spontaneous labor is awaited. If the patient is near term, she may be induced.

In the patient under 36 weeks gestation in whom

amniocentesis is impossible and who is clinically uninfected, expectant management is instituted until signs of infection develop. Tocolytics are sometimes used but with great trepidation since contractions may be a sign of infection. If increased gestational age is achieved and fetal lung maturation can be safely inferred to have occurred, the patient is allowed to go into labor or may be induced.

Patients are induced if the Gram stain of the amniotic fluid is positive for bacteria or if the patient develops signs of chorioamnionitis. If the patient is being given beta-mimetic agents for tocolysis, maternal and fetal tachycardia are not used as markers of chorioamnionitis because of the chronotropic effects of these agents on the maternal and fetal hearts.

MATERIALS AND METHODS

The data were obtained by reviewing the charts of patients admitted to the Maternal Special Care Unit at Yale-New Haven Hospital with the admitting diagnosis of PROM or who had the discharge diagnoses of PROM and Premature Birth Living Child during the period of January 1, 1981 to July 31, 1983. Patients were excluded from the study if they were over 36 weeks gestation at the time of PROM (n = 42), a twin gestation was present (n = 8), the patient delivered at another hospital (n = 4), the patient received corticosteroids (n = 2) or if the patient was admitted in active labor (n = 11). A total of 147 maternal charts and 140 neonatal charts were included in the study. 5 neonatal charts were lost of unavailable for review. There were 2 stillbirths.

The study group included clinic and private patients as well as transfers from one of the referring hospitals. Rupture of membranes was documented by fluid crystallization (fern test). No digital examinations were performed although some patients had been examined before admission to Yale-New Haven Hospital. Patients with questionable PROM who had negative fern tests were not included in the study. Patients were managed according to the Yale

protocol described above. Amniocentesis was performed under direct ultrasound guidance.

The data were collected and coded as shown in Appendix 2.

STATISTICAL METHODS

All the data were transferrred to IBM Standard Tape and analyzed by use of an IBM computer. Analysis of data was performed using x^2 and 2-tailed Student t tests.

RESULTS

(All Tables and Figures are in Appendix 1)

There were 147 patients with preterm PROM in this study. 84 (57%) were white, 50 (34%) were black, 8 (5.3%) were of Hispanic origin, and 5 (3.6%) were of other origin. 66 (45%) were nulliparas, and 80 (55%) had had one or more prior deliveries. 100 (71%) were transferred from one of the referring hospitals, 25 (18%) were local clinic patients, and 15 (11%) were local private patients. The small percentage of private local patiens might be explained by the fact that some private attending physicians will follow their PROM patients at home with bedrest and close attention to clinical signs of infection. Ages of the patients in the study

group ranged from 16 to 40 years. Amniocentesis was attempted in 87 patients (59.2%) and was successful in 77 (52.4%). 88% of amniocenteces were successful in obtaining amniotic fluid. 17 patients had two or more amniocenteses. The gestational ages at the time of PROM of the patients in the study group are shown in Figure 1.

Several maternal parameters were analyzed for correlation with a positive amniotic fluid culture to determine if any one factor could be predictive of a positive culture. Since uterine tenderness in not an objective or quantitative factor, it was not included in the analysis. The presence or absence of foul-smelling fluid on admission was rarely reconred on patient charts and was not included. Table 3 shows that admission maternal leukocyte counts (WBC count), neutrophil and band counts, uterine contractions, absolute neutrophil count, heart rate and temperature were not predicitve of positive amniotic fluid culture. Similarly, admission fetal heart rate was not predictive of a positive culture. Since a small percentage of patients had an interval of more than 24 hours between admission and amniocentesis, several clinical parameters at the time of the amniocentesis were analyzed. Table 4 shows that the following paremeters at the time of amniocentesis

were not predictive of a positive amniotic fluid culture: maternal age, gestational age, gravidity, parity, temperature, WBC count, neutrophil count, band count, absolute neutrophil count and uterine contractions. That is, these factors were no different in those patients with a negative amniotic fluid culture from those in patients with a positive culture.

As has been reported previously, (38,39) amniotic fluid obtained at amniocentesis can be Gram stained to look for the presence of bacteria. Of the 77 successful amniocenteses, the results of 76 Gram stains and 75 cultures were examined. Of the 75 cultures, 24 (32%) were positive. Two of the positive culture were considered contaminants because of the organisms involved (Staphylococcus coagulase -) and low colony counts. Neither of these had positive Gram stains. The organisms cultured are shown on Table 5. Table 6 shows that Gram stain of the amniotic fluid was 61.9% sensitive and 91.8% specific in predicting which patients were destined to have a positive amniotic fluid culture. The results of one Gram stain and one culture were not available for review. In one case not enough fluid was obtained for cultures to be obtained.

To determine whether a positive culture correlated with increased maternal morbidity, maternal clinical

parameters were followed from the time of amniocentesis to the time of delivery. A positive culture did not correlate with elevated antepartum temperature, elevated antepartum WBC count, increased neutrophil or band count or intrapartum temperature. A positive culture did, however, correlate with an increased administration of antibiotics antepartum and an increased rate of clinical diagnosis of amnionitis. Patients who had positive cultures underwent Cesarean sections more than those with negative cultures (36.4% versus 22.4%) but the difference was not statistically significant. Table 7 shows the correlation between culture result and subsequent maternal clinical course. One patient suffered a complication of amniocentesis (possible puncture of fetal vessel) without detrimental consequences to either mother or infant.

There were 145 live births and 2 stillbirths. 4 infant charts were unavailable for review, but the neonatal outcome was known for all births. 9 infants (6.6%) had positive blood cultures; 2 of them from mothers with positive amniotic fluid cultures, 2 from mothers with negative cultures, and 5 from mothers without amniocenteses. 2 infants with negative blood cultures had radiographically-proven pneumonia; one from a mother with a positive amniotic fluid culture

and one from a mother with no amniocentesis. 2 infant blood cultures were considered contaminants by the attending pediatricians. Both stillbirths were to mothers with positive amniotic fluid cultures. Statistically significant differences in gestational age at delivery and birth weight between infants of mothers with negative cultures and mothers with positive cultures are shown in Table 8.

There were 9 neonatal deaths, which with the two stillbirths gives a perinatal mortality rate of 7.5%. 5 deaths (3.4%) were attributable to prematurity, 2 to infection (1.4%) and 2 (1.4%) to multiple congenital abnormalities. Both stillbirths were believed to have been caused by amnionitis, hence the infection-related perinatal mortality rate was 2.7%.

Figures 2 and 3 show the Apgar scores of infants from mothers with positive and negative cultures at one and five minutes respectively. Table 9 shows statistically significant differences between both groups of infants. The percentage of infants with Apgar score of five or less at one minute is significantly higher in the group born to mothers with positive cultures. Similarly, significantly more infants born to mothers with positive cultures had Apgar scores at five minutes of seven or less.

Tocolytics were used in 76 patients. In 46.7% of these, delivery occurred one day or less after initiation of tocolytic agents. 78.3% of patients given tocolytics delivered less than 7 days after tocolytics were started, but delivery was delayed for one week or more in 22.7% of patients. These results are consistent with those recently reported by others (50,51). (See Figure 4). Since tocolytics were not started immediately after membrane rupture in most patients, the interval between PROM and delivery in some patients is greater than the interval between initiation of tocolytics and delivery.

DISCUSSION

Despite dramatic advances in the field of perinatology during the last decade, there has been no clear-cut progress in the development of an appropriate management strategy for preterm PROM. Clinicians are now equipped with several new resources: amniocentesis, corticosteroids, tocolysis, neonatal intensive care units.

The preterm patient with prematurely ruptured membranes is particularly prone to developing chorioamnionitis (9,21,22,42). Unfortunately, clinical signs develop only after the infection is usually well-established. Several studies (38,39,44-46) have shown that chorioamnionitis is associated with significantly increased neonatal morbidity and mortality. Thus, expeditious delivery seems indicated in cases where chorioamnionitis has been diagnosed (35,42,44-46). It is desirable to be able to predict which patients with PROM but without clinical signs of infection are destined to develop clinical chorioamnionitis, since efforts at prolonging pregnancy in the preterm PROM patient must rule out occult intrauterine infection.

In the patient with PROM, examination of amniotic

fluid obtained by amniocentesis allows the clinician to detect pulmonary maturity and infection. Unfortunately, in cases of PROM amniocentesis is successful only in about half of the patients (38-40). In the other half, amniocentesis cannot be performed or no fluid can be obtained.

The data in the present study agrees with these observations, since fluid was obtained in only 52.4% of the patients in the study group. In those patients in which amniocentesis was successful, though, admission clinical parameters or more importantly, parameters at the time of the amniocentesis were almost identical in women with positive amniotic fluid cultures to those in women with negative cultures. That is, there was no way to predict clinically what patients were destined to have a positive amniotic fluid culture. A positive culture was associated with a significantly worse neonatal outcome than a negative culture. Positive cultures, however, did not seem to be associated with increased maternal morbidity.

Statistically significant conclusions were difficult to draw in some instances because of varying gestational ages at the time of delivery between patients with negative and positive cultures and by difficulties

in diagnosing and grading RDS. There were significantly more cases of moderate and severe RDS in infants from mothers with positive cultures, but the mean gestational age at delivery and mean birth weight of infants in this group was significantly lower than in the group with negative cultures. Both gestational age and birth weight are significant variables in the development of RDS.

A larger percentage of patients with positive cultures underwent cesarean sections than those with negative cultures, but this difference could have been due to the earlier gestational ages of the group with positive cultures and its correspondingly greater incidence of breech and transverse lies.

Although amniocentesis is not an entirely safe procedure, the complication rate in our study was very low (1.1%) and no major complications were seen. Unfortunately, results of amniotic fluid cultures take 48 hours or more to be reported. Gram stain of the amniotic fluid provied a rapid way of detecting the presence of amniotic fluid colonization. Results from this study show that Gram stain of the fluid was 62% sensitive and 92% specific in predicting a positive culture. Other authors (38,39) have reported slightly

higher sensitivities and slightly lower specificities.

The accuracy of the Gram stain is crucial in managing the patient with PROM. A false-positive Gram stain may lead to an inappropriately early delivery resulting in potentially avoidable complications of prematurity. A false-negative Gram stain may lead to hazardous prolongation of intrauterine life in the presence of colonization, although it is unclear whether there is any real advantage in delivery before infection is clinically evident (17).

One of the criticisms of conservative management of preterm PROM is that although infection is not a serious problem, delivery cannot be delayed sufficiently in most cases to allow for significant fetal maturation (17,34). In this study nearly half the patients delivered within a day of initiation of tocolytics, but in almost a quarter of them delivery was delayed for more than one week. At present it is not possible to predict which patients will respond favorably to tocolytic therapy.

In summary, amniocentesis should be included in the evaluation of the preterm patient with PROM in whom a delay in delivery is being considered in the management plan. Unresolved problems in the conservative

management of preterm PROM include the large percentage of patients in which amniocentesis is not feasible or is unsuccessful, inability to delay delivery in some cases even in the absence of infection, and inaccuracy of the Gram stain. However, Gram stain of the amniotic fluid obtained by amniocentesis is at present the only way to obtain rapid information about the presence or absence of amniotic fluid colonization in cases of PROM.

APPENDIX 1

TABLE 1: INCIDENCE OF PROM

Author	# Pregnancies	# PROM	% PROM	Definition of PROM
Clark & Anderson (1)	33,022	1,009	2.1	+++
Lanier et al (2)	7,637	473	6.2	ROM outside the hospital
Breese (3)	44,723	2,862	6.4	ROM 1 hr before onset of labor
Russel & Anderson (4)	31,865	2,645	8.3	ROM before onset of labor
Burchell (5)	18,138	1,795	9.9	ROM 1 hr before onset of labor
Gunn et al (6)	17,562	1,884	10.7	ROM before onset of labor
Lebherz et al (7)	25,427	2,923	11.5	ROM 1 hr before onset of labor
Rovinsky & Shapiro (8)	30,336	3,793	12.5	ROM 1 hr before onset of labor

TABLE 2: RELATIONSHIP BETWEEN PROM AND DECREASED RDS (24)

A. Studies showing no association

Liggins: Modern Perinatal Medicine, 1974
Jones: NEJM 292:1253, 1975
Dimmick: Obstet Gynecol 47:56, 1976
Christensen: Obstet Gynecol 48:670, 1976
Dluholucky: Arch Dis Child 51:420, 1976
Bada: Pediatr Res 10:420, 1976
Lee: Pediatr Res 10:463, 1976
Barrada: Am J Obstet Gynecol 129:25, 1977
Quirk: Am J Obstet Gynecol 134:768, 1979
Taeusch: Pediatrics 63:64, 1979
Schreiber: Am J Obstet Gynecol 136:92, 1980

B. Studies suggesting a beneficial effect

Alden: Pediatrics 50:40, 1972
Yoon: Pediatrics 52:161, 1973
Chiswick: Lancet 1:100, 1973
Gluck: Am J Obstet Gynecol 115:539, 1973
Richardson: Am J Obstet Gynecol 118:115, 1974
Bauer: Pediatrics 53:7, 1974
Cohen: J Pediatr 98:1007, 1977
Berkowitz: Am J Obstet Gynecol 131:503, 1978
Sell: Obstet Gynecol 49:167, 1977
Thibealt: Am J Obstet Gynecol 129:43, 1977
Seidl: Eur J Ob Gyn & Rep Biol 7:257, 1977
Worthington: Obstet Gynecol 49:275, 1977
Miller: Am J Obstet Gynecol 132:1, 1978
Obladen: Am J Obstet Gynecol 135:1079, 1979

TABLE 3: ADMISSION DATA ON PATIENTS WITH SUCCESSFUL AMNIOCENTESES[+] *

PARAMETER	(-) CULTURE	(+) CULTURE
Mean temperature	98.8 ± 0.81	98.5 ± 0.62
Mean # contractions in 10 min	1.04 ± 1.43	1.02 ± 1.41
Mean WBC count (x1000)	11.1 ± 3.04	10.7 ± 3.31
Mean neutrophil count (%)	72.8 ± 8.18	71.6 ± 8.20
Mean band count (%)	5.35 ± 4.70	7.23 ± 6.49
Mean absolute neutrophil count (x1000)	8.84 ± 3.35	8.57 ± 3.07
Mean fetal heart rate	146 ± 17.3	144 ± 11.6
Mean maternal heart rate	88.5 ± 13.6	91.9 ± 14.2

[+]Differences in parameters between groups are all statistically not significant.

*All means are given as N ± S.D.

TABLE 4: DATA AT TIME OF AMNIOCENTESIS OF PATIENTS WITH POSITIVE AND NEGATIVE AMNIOTIC FLUID CULTURES*

PARAMETER	(-) CULTURE	(+) CULTURE
Mean maternal age	26.4 ± 5.49	27.4 ± 4.98
Mean gestational age	31.2 ± 2.71	30.0 ± 3.43
% primigravidas	25.8	13.8
% nulliparas	51.9	24.5
Mean temperature	98.5 ± 0.58	98.8 ± 0.76
Mean WBC count (x1000)	11.0 ± 3.50	10.8 ± 3.81
Mean neutrophil count (x1000)	71.3 ± 9.67	73.5 ± 11.3
Mean band count (x1000)	8.30 ± 6.85	6.45 ± 4.85
Absolute neutrophil count (x1000)	8.87 ± 3.36	8.81 ± 3.65
% having contractions	43.0	36.0

*Differences in parameters are not statistically significant.

TABLE 5: ORGANISMS CULTURED FROM AMNIOTIC FLUID*

Streptococcus viridans	4
Escherichia coli	4
Diphtheroid sp	4
Peptostreptococcus	3
Enterococcus	3
Haemophilus vaginalis	3
Fusobacterium nucleatum	2
Bacteroides fragilis	2
Group D Streptococcus	2
Haemophilus influenzae	2
Group B streptococcus	1
Neisseria gonorrheae	1
Proteus mirabilis	1
Candida albicans	1

*Some cultures grew multiple organisms

TABLE 6: ACCURACY OF GRAM STAIN OF AMNIOTIC FLUID IN PREDICTING A POSITIVE AMNIOTIC FLUID CULTURE*

TRUE POSITIVES	13		
		SENSITIVITY	61.9%
FALSE NEGATIVES	8		
TRUE NEGATIVES	45		
		SPECIFICITY	91,8%
FALSE POSITIVES	4		

*Results of one Gram stain were unavailable

TABLE 7: CULTURE RESULT AND SUBSEQUENT MATERNAL COURSE*

	(-) culture	(+) culture	
Highest antepartum temperature	99.2 ± 0.77	99.4 ± 0.88	N.S.
Highest antepartum WBC count (x1000)	13.6 ± 4.26	12.3 ± 4.08	N.S.
Highest antepartum neutrophils (%)	70.9 ± 13.3	71.0 ± 10.0	N.S.
Highest intrapartum temperature	99.6 ± 1.08	99.6 ± 1.11	N.S.
Cesarean section rate	22.4%	36.4%	N.S.
Clinical diagnosis of amnionitis	41.1%	68.5%	$p < 0.05$
Days between ROM and delivery	11.6 ± 18.1	3.64 ± 5.30	$p < 0.05$
Gestational age at time of delivery (weeks)	32.8 ± 2.68	30.5 ± 3.55	$p < 0.01$
Antibiotics administered antepartum	14.3%	41.0%	$p < 0.05$

* All figures (except %'s) are means.

TABLE 8: MEAN GESTATIONAL AGE AT DELIVERY AND MEAN BIRTH WEIGHT OF INFANTS OF PATIENTS WITH POSITIVE AND NEGATIVE AMNIOTIC FLUID CULTURES*

	(-) culture	(+) culture
Mean gestational age at delivery (weeks)	30.5 ± 3.55	32.8 ± 2.68
Mean birth weight (grams)	1885 ± 524.4	1512 ± 620.0

*$p < 0.05$

TABLE 9: STATISTICALLY SIGNIFICANT DIFFERENCES IN INFANTS BORN TO MOTHERS WITH POSITIVE AND WITH NEGATIVE AMNIOTIC FLUID CULTURES

	(-) culture	(+) culture	
$Apgar_1 < 5$ or stillbirth (%)	26.5	65.2	$p < 0.01$
$Apgar_1 \geq 5$ (%)	73.5	34.8	
$Apgar_5 < 7$ or stillbirth (%)	21.3	60.8	$p < 0.05$
$Apgar_5 \geq 7$	78.7	39.2	
Antibiotics administered to infant (%)	70.2	100.0	$p < 0.01$

FIGURE 1: GESTATIONAL AGE AT THE TIME OF RUPTURE OF MEMBRANES

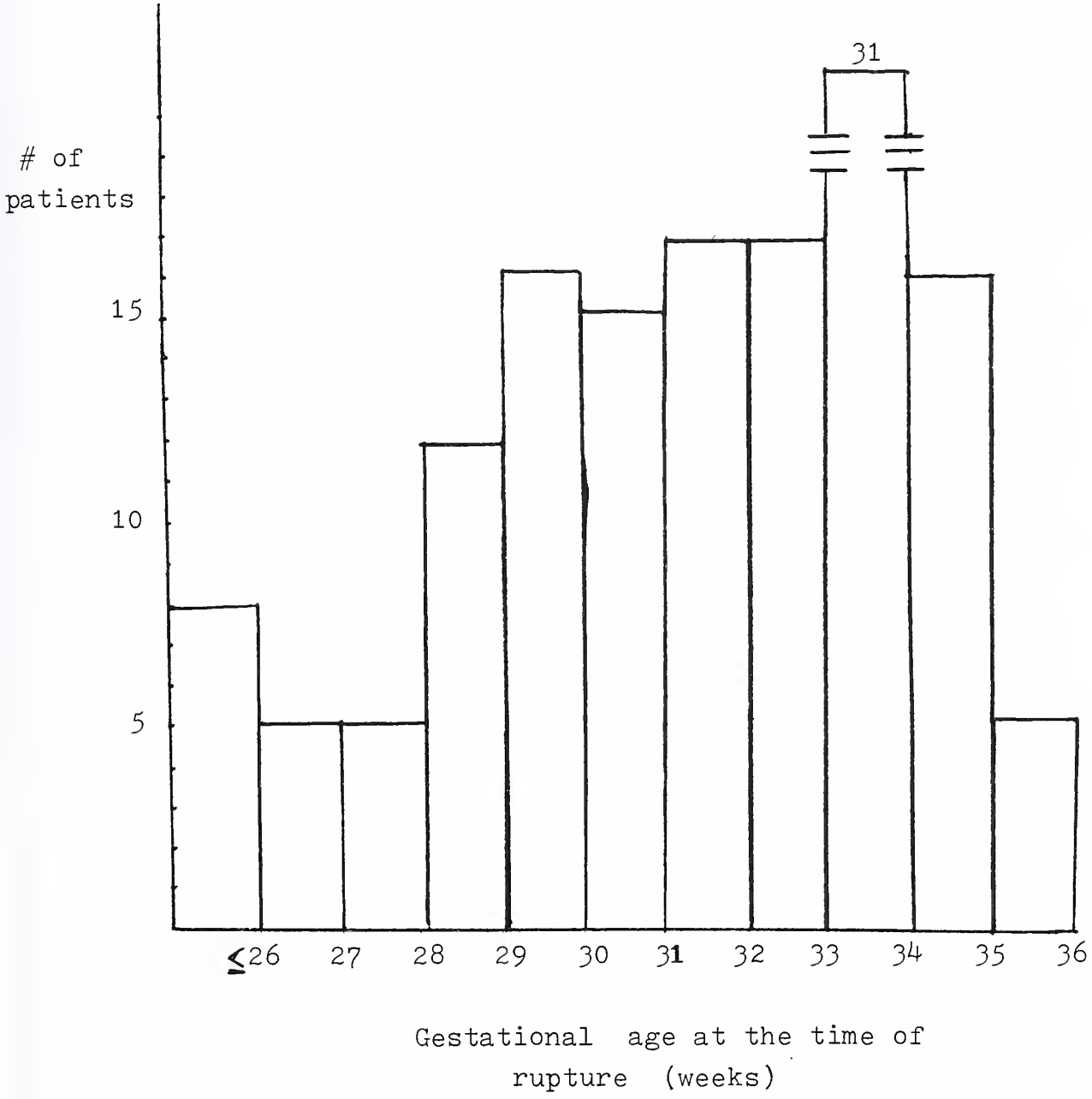


FIGURE 2: APGAR SCORE AT ONE MINUTE BY AMNIOTIC FLUID CULTURE RESULT

= negative culture

= positive culture

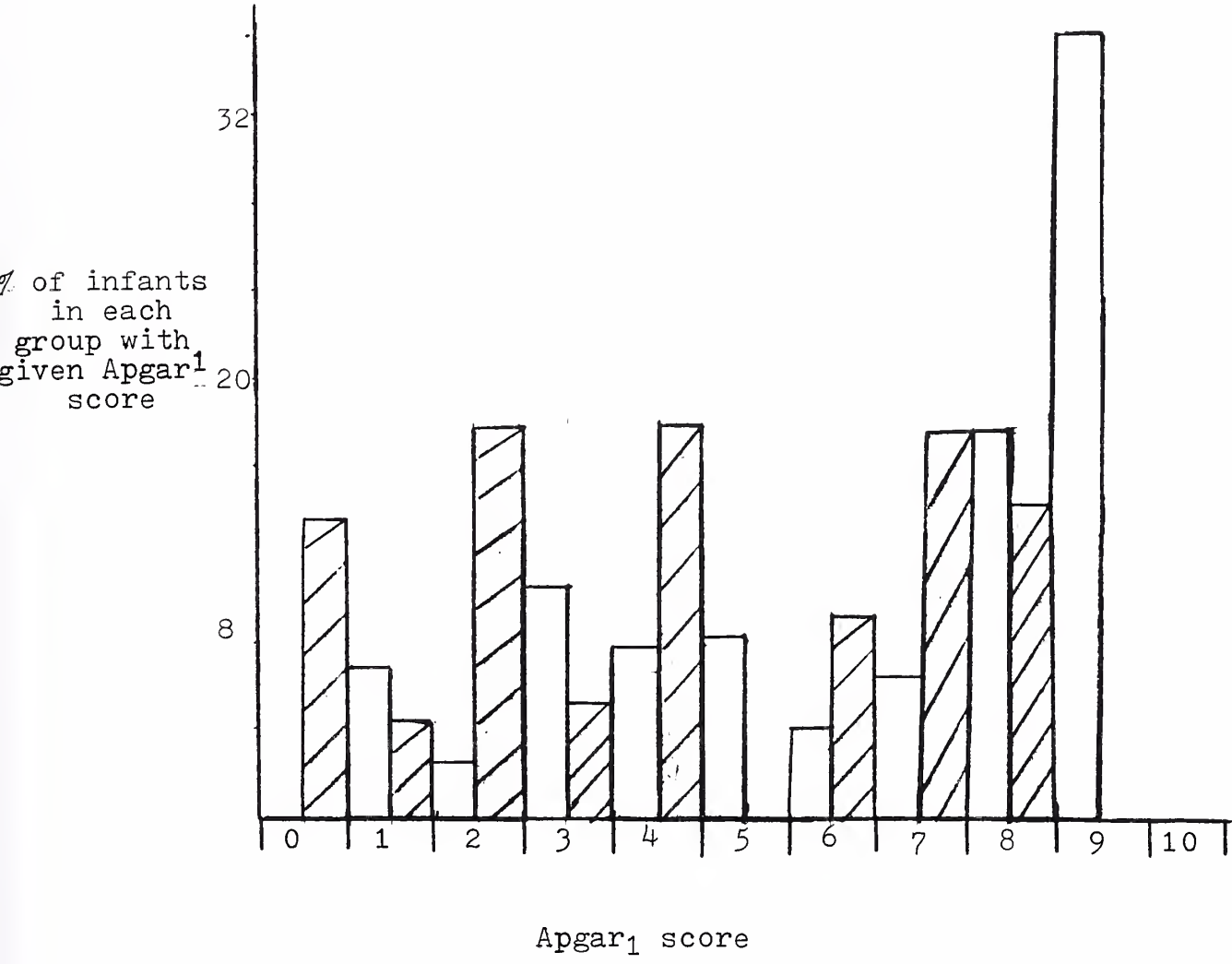


FIGURE 3: APGAR SCORE AT FIVE MINUTES BY AMNIOTIC FLUID CULTURE RESULT

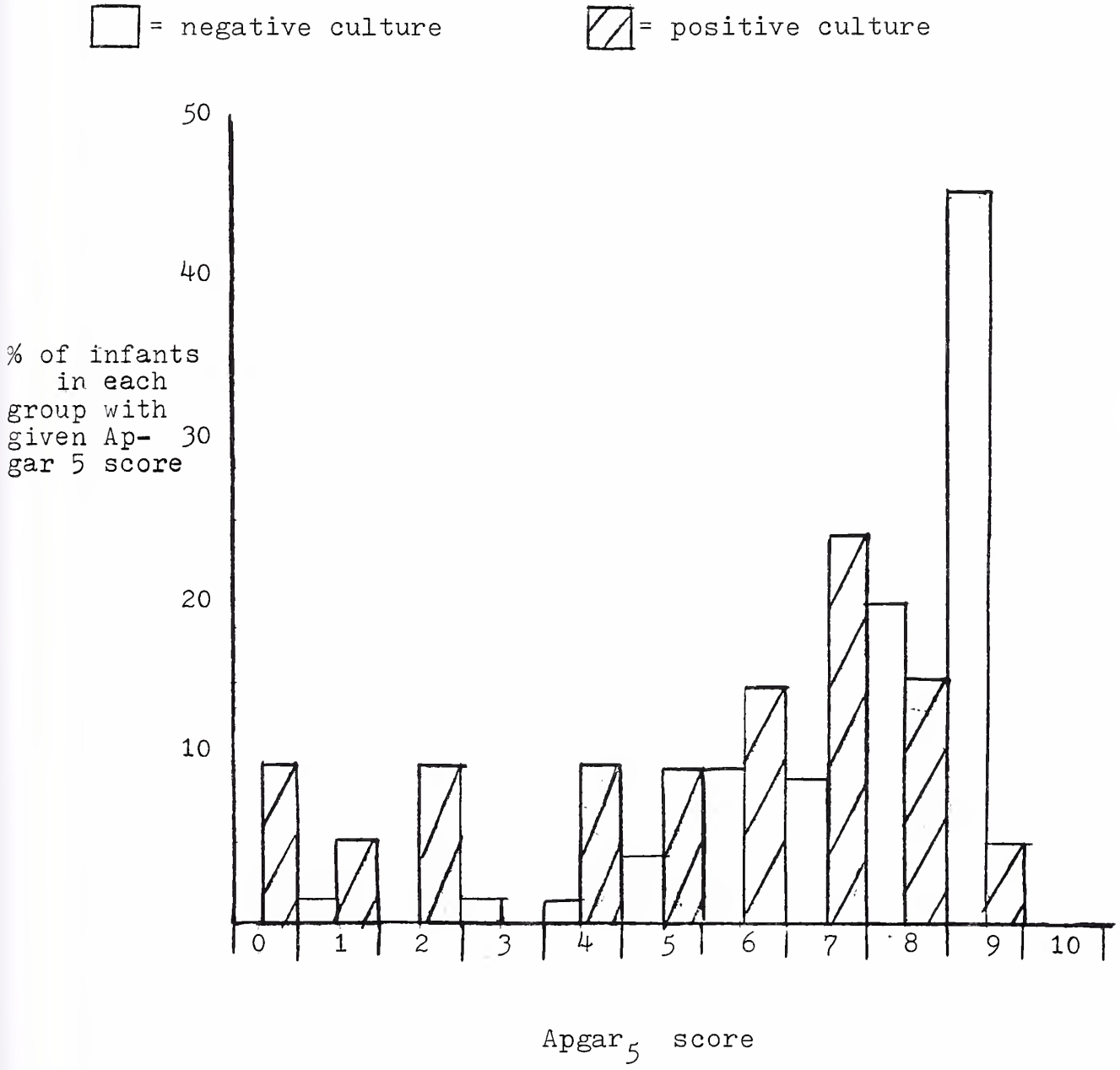
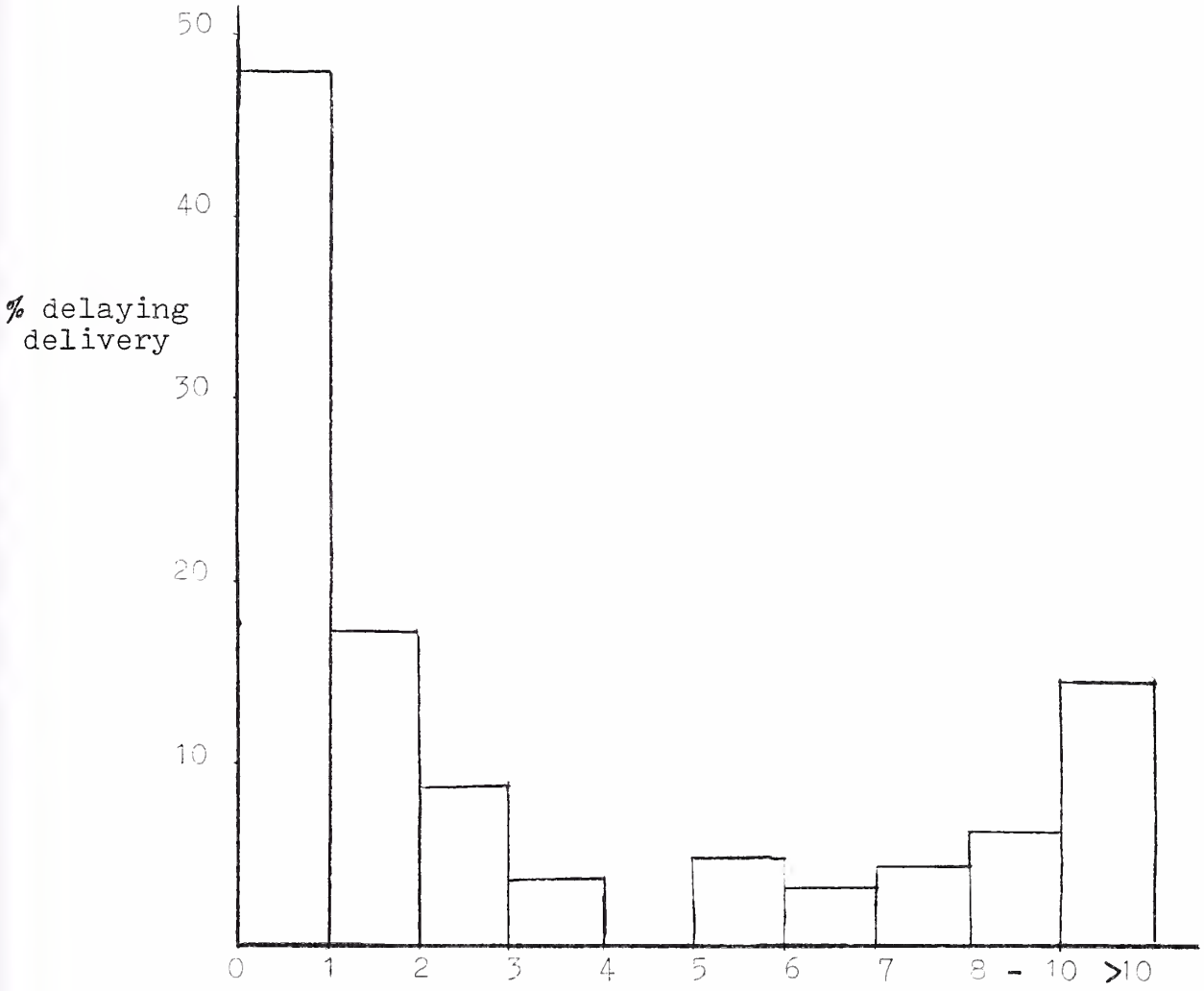


FIGURE 4: INTERVAL BETWEEN INITIATION OF TOCOLITICS AND DELIVERY



APPENDIX 2

STUDY ID __ __ __ __
1 4

NAME __ __ __ __ __ __ __ __ __ __ __ __ __ __
5 18

UNIT NUMBER __ __ - __ __ - __ __
19 25

AGE __ __
26 27

RACE __ 1-White; 2-Black; 3-Hispanic;
28 4-Other; 5-Not recorded

GRAVIDITY __ 1-Primigravida; 2-Multigravida; 3-No available
29

PARITY __ 1-Nullipara; 2-Multipara; 3-Not available
30

BEST GA AT TIME OF PROM __ __ . __
31 33

DATE OF PROM __ __ / __ __ / __ __
34 39

TIME OF PROM __ __ : __ __
40 43

PELVIC EXAMINATION PRIOR TO LABOR __ 1-Yes; 2-No; 3-Not recorded
44

PATIENT CLASSIFICATION __ 1-Transfer; 2-Clinic-local;
45 3-Private-local

ADMISSION TO Y-NHH

Temp on labor floor admission __ __ __ . __
46 47 48 49

contractions in 10 minutes __
50

Foul discharge: 1-Yes; 2-No;
3-Not recorded __
51

Fetal heart rate on admission __ __ __
52 53 54

Maternal pulse on admission __ __ __
55 57

B-2 Agents administered prior to pulse and FHR recording 1-Yes 2-No __
58

Vaginal culture for group B strep
1. Negative 2. Positive 3. Not done __
59

W B C __ __ . __
60 62

Hematocrit __ __ . __
63 65

Polys __ __
66 67

Bands __ __
68 69

Card # 1
72

STUDY ID _ _ _ _ (1–4)

LYMPHOCYTES _ _ (5–6)

MONO _ _ (7–8)

BASO _ _ (9–10)

EOS _ _ (11–12)

Was U/S done 1-Yes; 2-No 3-Not Stated _ (13) Date _ _/_ _/_ _ (14–19)

E F W _ _ _ grams (20–23)

PLACENTA 1-Anterior; 2-Posterior 3-Not Stated _ (24)

Gestational age by dates _ _._ (25–27)

Gestational age by clinical ex (LMP + size + quickening) _ _._ (28–30)

Gestational age by early U/S (Prior to 28 weeks) _ _._ (31–33)

Gestational age by U/S at PROM _ _._ (34–36)

AMNOCENTESIS # 1

Amniocentesis 1-Performed; 2-Not attempted 3-Not Stated _ (37)

Fluid Obtained 1-Yes; 2-No _ (38)

Date of Tap (If fluid obtained _ (39) _ _/_ _/_ _ (40–44)

Temp at time of tap _ _._ (45–48)

WBC at time of tap _ _._ (49–51)

Segs _ _ (52–53)

Bands _ _ (54–55)

Was the patient contracting 1-Yes 2-No _ (56)

If Amniocentesis was not performed the reason was 1-Considered unsafe _ (57) 2-Other _____

_____

Amniotic fluid: 1-Clear
2-Bloody
3-Meconium
4-Not Stated
5-No fluid
58

Complication of amniocentesis 1-Yes
2-No
59 _____

L/S Ratio
60 61

Bacteria gram stain 1-GPC
2-GNR
3-GNC
4-GPR
5-Other combinations
6-No bacteria
7-Not stated
62 _____

WBC gram stain 1-Absent
2-Present-few
3-Moderate
4-Many
5-Not Stated
63

Culture 1-Negative
2-Positive
3-Not Stated
4-Not Obtained
64

Did the patient have more than one amniocentesis 1-Yes
2-No
65

AMNIOCENTESIS # 2

INDICATION
1-Labor
2-Routine
3-Other
66 _____

Days between first and second amniocentesis
67

Fluid Obtained 1-Yes; 2-No
68

CARD # 2
72

STUDY ID # ___ 1-3

Date of Tap (If fluid obtained ___/___/___ 4-9

Temp at time of tap ___.___ 10-13

WBC at time of tap ___.___ 14-16

Segs 17-18

Bands 19-20

Was the patient contracting 1-Yes 2-No 21

Amniotic fluid: 1-Clear 2-Bloody 3-Meconium 4-Not Stated 5-No fluid 22

Complication of amniocentesis 1-Yes 2-No 23 _____ _____

L/S Ratio ___.___ 24-25

Bacteria gram stain 1-GPC 2-GNR 3-GNC 4-GPR 5-Other combinations 6-No bacteria 26 _____

WBC gram stain 1-Absent 2-Present-few 3-Moderate 4-Many 5-Not Stated 27

Culture 1-Negative 2-Positive 3-Not Stated 4-Not Obtained 28 _____

Did the patient have more than two amniocentesis 1-Yes 2-No 29

AMNIOCENTESIS #3

INDICATION
1-Labor
2-Routine — 30
3-Other

Days between second and third amniocentesis — 31

Fluid Obtained 1-Yes; 2-No — 32

Date of Tap (If fluid obtained — 33 __/__ __/__ 38

Temp at time of tap — 39 __ __.42

WBC at time of tap — 43 __.45

Segs — 46 47

Bands — 48 49

Was the patient contracting 1-Yes 2-No — 50

Amniotic fluid: 1-Clear 2-Bloody 3-Meconium 4-Not Stated 5-No fluid — 51

Complication of amniocentesis 1-Yes 2-No — 52 _____ _____

L/S Ratio — 53.54

Bacteria gram stain 1-GPC 2-GNR 3-GNC 4-GPR 5-Other combinations 6-No bacteria — 55 _____

WBC gram stain 1-Absent 2-Present-few 3-Moderate 4-Many 5-Not Stated — 56

Culture

1-Negative
2-Positive
3-Not Stated
4-Not Obtained

57 _____

INDICATION FOR DELIVERY

58

1-Labor unresponsive to tocolytes
2-Amnionitis
3-Mature L/S ratio
4-Fetal distress
5-Bacteria in gram stain
6-Labor, no tocolytics
7-Other

_____
_____
_____

LABOR

59

1-Spontaneous
2-Induced
3-No labor
If 2 or 3 _____

Delivery Date

60 __/__ __/__ 65

Type of Delivery

66

1-Vaginal sponatenous
2-C/Section
3-Forceps
4-Other

Weight

67 __ __ 70

Tocolytics used

1-$MgSO_4$
2-Beta-Mimetics
3-None

71

CARD # 3
72

STUDY ID #

1 __ __ 3

Apgar 1 minute

4 5

Apgar 5 minutes

6 7

Baby Unit # _ _ _ - _ _ - _ _ _ _ _ _
8 14

Antepartum administration of antibiotics 15
1-Yes
2-No
3-Other Indications

Interval between PROM - last successful Tap _ _ days
16 17

Interval between PROM - Delivery _ _ _ days
18 20

Clinical diagnosis of amnionitis _____
1-Yes; 2-No 21 _____

Highest antepartum temp _ _ . _
22 25

Highest FHT (if no tocolytis) _ _ _
26 28

Highest antepartum WBC _ . _
29 31

Polys _ _
32 33

Bands _ _
34 35

Date _ _ / _ _ / _ _
36 41

Highest intrapartum temp _ _ . _
42 45

Interval between PROM and clinical diagnosis of amnionitis _ _ days
46 47

Interval between PROM and initiation of tocolytic agents _ _ days
48 49

Interval between initiation of tocolytic - delivery _ _ days
50 51

Post-partum Maternal infection 52
1-None 2-Endometritis 3-UTI
4-Wound infection 5-Pneumonia 6-Other _____

Highest post-partum temperature _ _ . _
53 56

Were antibiotics used post-partum 57
1-Yes; 2-No
Indication _____

Blood Cultures (Maternal)
1-Negative
2-Positive
3-Not done — 58

BABY

Baby sex
1-Male
2-Female
3-Not available — 59

Gestational age by physical exam — 60 — . — 62

IUGR: 1-Yes; 2-No; 3-Unknown — 63

Sepsis: 1-Yes; 2-No; 3-Unknown — 64

Foul smelling newborn
1-Yes; 2-No; 3-Unknown — 65

Blood Cultures
1-Negative
2-Positive _____
3-Not Done — 66

CSF Culture
1-Negative
2-Positive _____
3-Not done — 67

Antibiotics administered to the baby
1-Yes; 2-No; 3-Unknown — 68

RDS
1-No; 2-Mild; 3-Moderate;
4-Severe; 5-Unknown — 69

Mechanic ventilation
1-No; 2-CPAP only; 3-IMV; 4-Unknown — 70

CARD # 4 — 72

STUDY # ___ 1 — ___ 3

Maximum FIO_2 ___ 4 ___ 5

Number of days in mechanic ventilation ___ 6 ___ 7

Intracranial hemmorhage ___ 8 _____ Grade
1-Yes; 2-No; 3-Not evaluated; 4-Unknown

Necrotizing entercolytis ___ 9
1-Yes, 2-No; 3-Unknown

Other Baby Complications ___ 10 _____
1-Yes; 2-No; 3-Unknown _____

NICU days of hospitalization ___ 11 — ___ 13

Neonatal deaths ___ 14
1-Yes; 2;-No; 3-Unknown

Cause of neonatal death ___ 15 _____
1-Prematurity; 2-Infection; 3-Other _____

Direct cause of death _____
_____

CARD # 5
20

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